GRAVITY, CALCIUM, AND BONE: UPDATE, 1989

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This update highlights some of the results of recent short-term flight and ground-based experiments that have contributed new insight into skeletal adaptation, calcium metabolism, and growth processes in 0 g. After 6 months in space, bone demineralization, invariably involving the os calcis (20), was found not to extend to the lumbar spine in 4 exercising cosmonauts (3). A flight experiment in the Space Shuttle crew has documented the early events in the calcium endocrine system during spaceflight (12).

On the ground, brief (<35 days) and long-term (>4 months) bed rest studies of healthy volunteers in the head-down tilt (HDT) model of weightlessness have been completed. The skeleton of the adult male responds more rapidly to unloading than previously recognized (2). Regional changes in bone density can be quantified in only 30 days, are highly individual, and follow the direction of gravitational forces in the HDT model during inactivity (1). Bone biopsy results in healthy volunteers after bed rest (11) differ from results in paraplegics from the same sampling site (21).

Flight experiments in growing rats reveal changes in the composition of bone mineral and matrix in the femur postflight that were found to be highly regional and suggestive of an effect of gravity on mineral distribution (10). These observations may be relevant to the results from an earlier Cosmos flight where artificial gravity in space was found to maintain bone strength, but not to correct the radial growth deficit (19).

Mineral in the Lumbar Spine

Ever since Krolner and Toft reported a reduction (–3.8%) in the average density of the 2nd to 4th lumbar vertebrae following therapeutic bed rest in 28 patients suffering from prolapsed intervertebral discs, there has been some concern that vertebrae in bed rest subjects and space travelers may demineralize (7). Fortunately, no significant changes were observed by Drs. Cann and Oganov, who used quantitative computer tomography to quantify the mineral content of the body of the 2nd lumbar vertebra of 4 cosmonauts before and after 6 months in space (3). These data have not completely erased the concern of osteoporosis in the lumbar spine because the Cosmonauts exercised daily.

Nevertheless, nonexercising bed rest subjects have also failed to show reduced bone density in the lumbar spine. LeBlanc et al. found no change in the density of the 2nd through 4th lumbar vertebrae in 5 of 6 subjects after 5 weeks of bed rest (horizontal); one showed a 3% decrease (8). Oganov et al. reported average increases to 12.6% in density of the spongiosa of the lumbar vertebrae of 3 bed rest subjects after 120 days in a –5° head-down tilt position (HDT) (14).

We used dual photon absorptiometry to measure the density of the 2nd through 4th lumbar vertebrae before and after 30 days HDT (–6°). Subjects were participating in a study designed to test the effect of isokinetic and isotonic exercise on orthostatic tolerance (5). Our results, shown as percent change in the histogram in Fig. 1, revealed no differences in 17 subjects, irrespective of the exercise group. Two subjects showed changes in opposite directions (–7 and +10%), well outside the error of the test.

Calcium Endocrine System

To identify factors that could have contributed to the change in lumbar spine mineral in 2 of 19 subjects, we examined the diet and a variety of parameters known to influence bone metabolism. Table I enumerates the values in these two subjects before and after bed rest. Figures 2a and 2b illustrate changes in circulating hormone concentrations that may be related to the alteration in lumbar spine density. None of the values except for serum parathyroid hormone (PTH) reached values outside the normal range. Combined increases in serum PTH and weight loss (4) favored decrease in lumbar spine mineral; the opposite changes were associated with an increase. These data are consistent with the known effects of PTH to enhance bone resorption. The precise role of serum 1, 25-dihydroxyvitamin D in the change in bone mineral content is not clear.

The early response of the calcium endocrine system in 4 astronauts was documented in serum obtained before, during, and after 7 days in space on the SL2 mission (12). The published data are summarized in Fig. 3. An increase in the vitamin D hormone, 1, 25-D, within the first 36 hours of launch was the only significant change, although trends toward increases in total serum calcium and phosphorus and decreases in bioactive PTH were present in 3 astronauts. Possible explanations for the early increase in 1, 25-D include perturbations during launch, transient lack of dietary calcium associated with space motion sickness, a nonspecific stimulation of renal 1-alpha hydroxylase connected with fluid shifts, or a specific

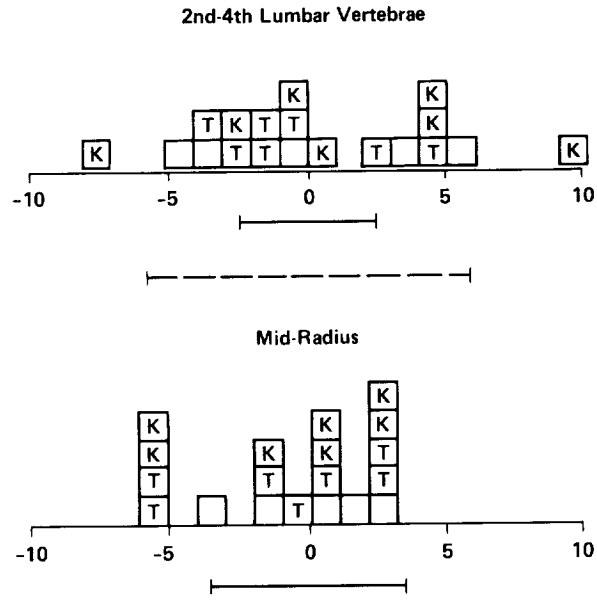

Figure 1. Percent change in density of the lumbar spine and mid-radius of 19 men referenced to each subjects basal level (0). Distribution was not affected by exercise (isotonic = T, isokinetic = K, no exercise = blank). The error of the tests are indicated by the bars, ⊢⊣ and $2 \times \sqrt{2} \times$ coeff. of variation, by (⊢------⊣).

Table I. Comparison of clinical data in two exercising subjects who showed opposite changes in lumbar spine density after 30 days head-down tilt bed rest.

	A			B		
Study day, from 1st bed rest day	-5	4	27	-5	4	27
Age, years	42			37		
Weight, kg	68		68.6	83.8		82
Height, cm	171			183		
Plasma volume,[a] ml/kg	46.3		40.5	48.2		39.9
Body fat,[a] %	7.7			8.0		
Serum						
Total calcium, mg/dl	9.1		8.8	9.9		9.8
Ionized calcium, mg/dl	4.20		5.00	4.88		4.96
Total protein, g/dl	7.2		7.0	7.2		7.2
Phosphorus, mg/dl	2.0		3.2	2.3		2.3
Parathyroid hormone,[b] pg/ml	20	24	17	24	59*	44
1, 25-dihydroxyvitamin D, pg/ml	16	17	37	33	28	30
Cortisol,[c] ug/dl	16.9		15.6	9.5		11.3
Testosterone,[c] total, ng/ml	882			871		
Testosterone,[c] free, ng/dl	25			22.2		
Urine						
Creatinine clearance, ml/min/1.73m^2	128		123	108		118
Calcium, mg/24 hr	229		165	182		301
Hydroxyproline, mg/24 hr	21		15	36		42
Diet during study[d]						
Calories, kCal/kg	42		45	34		36.8
Calcium, mg	1281		1398	1274		1431
Phosphorus, mg	1816		1959	1883		2020
Sodium, mg	5756		5941	5615		5976
Protein, g	117		119	114		119
Bone density[e]						
Radius, gm/cm	1.304		1.337	1.422		1.434
Lumbar spine, L2-4, gm/cm^2	1.175		1.293	1.875		1.725

Analysis of [a] by J. Greenleaf, [b] by R. Marcus, [c] by C. Wade, [d] by R. Williams, and [e] by M. Powell.
*Above the normal range.

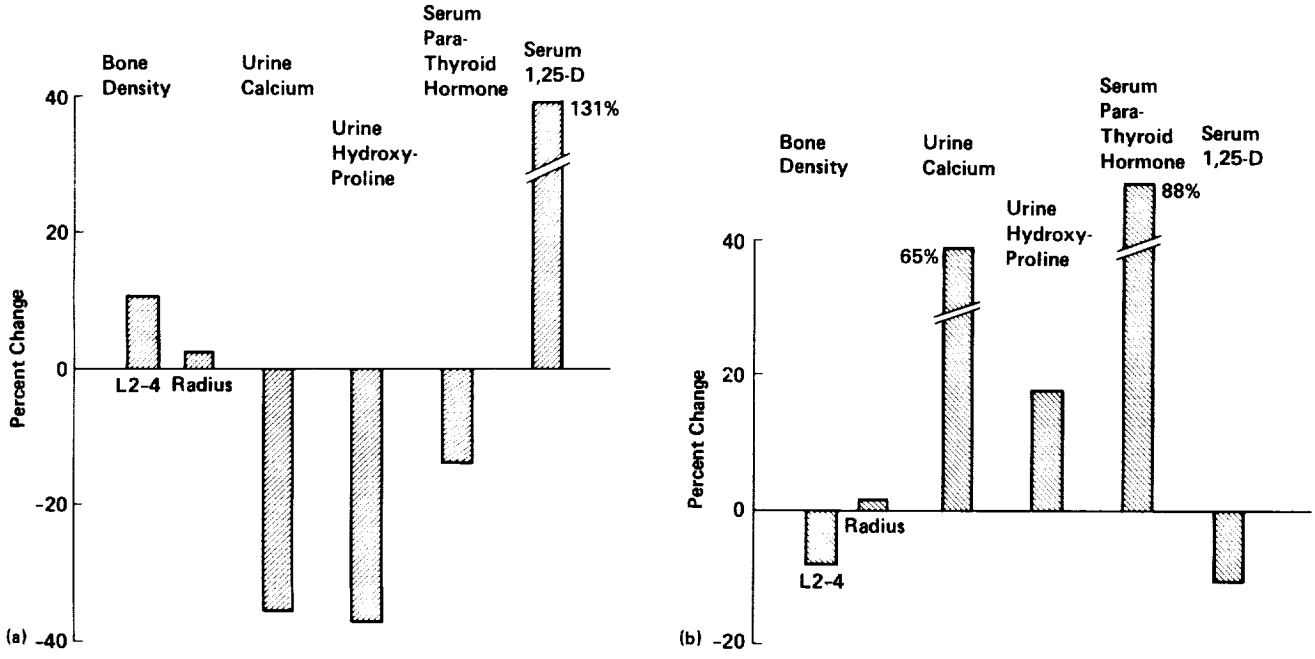

Figure 2. Changes in some parameters of calcium homeostasis, referenced to pre-bed rest levels, in subject A (a) who showed an increase, and subject B (b) who showed a decrease in lumbar spine density after 30 days bed rest. Of interest, both subjects performed isokinetic exercise for 30 min twice daily (5).

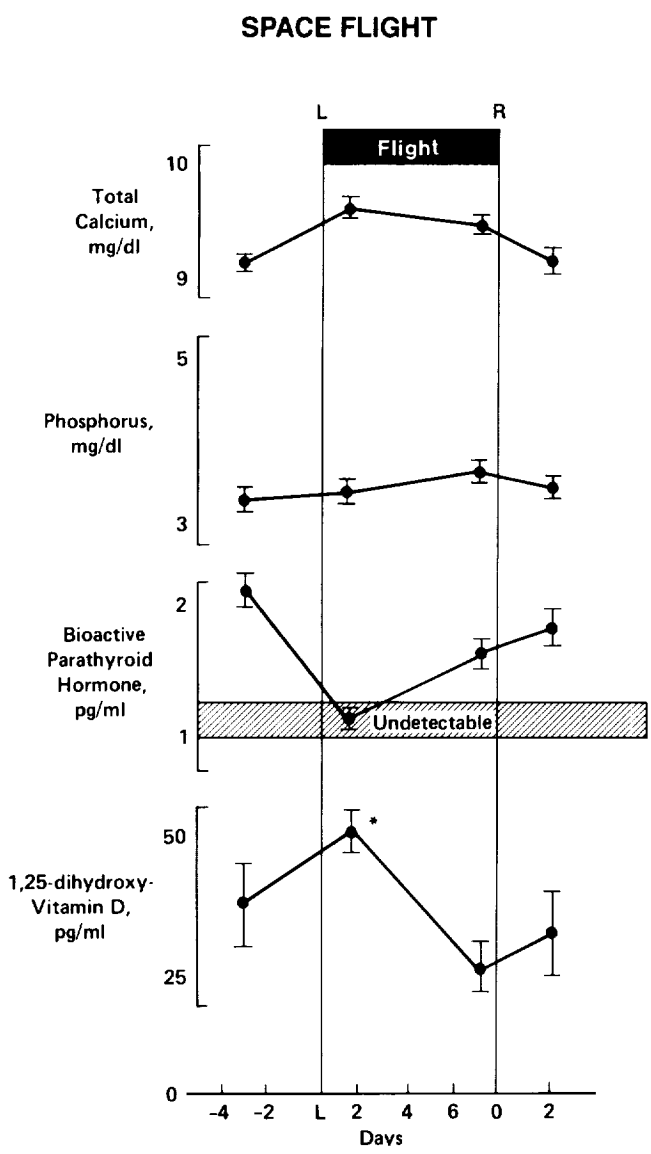

Figure 3. Mean values (±SE) in the serum of four astronauts obtained 1 week before, during, and the first week after launch (L) of a 7-day shuttle spaceflight (SL2) (data replotted from reference 13).

response in vitamin D metabolism to a change in a biomechanical stimulus originating in bone or muscle. Differences in the values during the first 24 hours did not seem to affect 7-day values, which are in the direction of being lower, but are not different from preflight values. The important contribution of these few samples taken during a flight is the preliminary knowledge that biologically active PTH, undetectable in serum after 36 hours in space, was not increased after 7 days, nor was 1, 25-D. While excesses of serum PTH cannot be responsible for the early mobilization of bone calcium, transient increase in 1, 25-D may be.

The above short-term data in flight differs from the results of a 7-day HDT study conducted at Ames Research Center, in which no changes were found during the first 36 hours. However, after 7 days, the trends to lower serum PTH and 1, 25-D in flight and on the ground were similar (11). The long-term Soviet bed rest study shows changes compatible with parathyroid hyperplasia with increases in serum calcium and PTH (especially after 49 days), suggestive of differences in early and late responses in the calcium endocrine system (13).

Of interest, in the Soviet bed rest study, were early increases in serum levels of calcitonin, an inhibitor of bone resorption, that gradually decreased to lower than basal levels after 3 months. Given the variations in both assay methods and bed rest protocols, the status of the calcium endocrine system, at least, after the first week in space or bed rest in healthy individuals, remains uncertain.

Bone Morphology

If newer concepts in the role of PTH and 1, 25-D in the processes of bone remodeling are correct, i.e., that PTH governs the differentiation and number of bone cells, and 1, 25-D, cell activity (9), the pattern of circulating hormone levels from the SL2 mission suggests the following early sequence of events: enhanced mobilization of calcium from bone related to the increase in 1, 25-D followed by suppressed mineralization in unloaded bones after a few days, with no increase in the number of osteoclasts or osteoblasts. Standard post mortem examination of some of the bones of 3 Cosmonauts after 28 days in space showed normal histology, fewer vascular channels than a control sample, and some increase in the porosity of the femoral epiphysis and diaphysis, but not in the rib, vertebrae, or calcaneus (16). Jowsey's analysis of the iliac crest of patients after 4-17 days horizontal bed rest for conditions unrelated to the skeleton, demonstrated reduced bone formation and no difference in the extent of resorption surfaces from normal in 11 of 14 patients. Cell counts are not in the report (6).

Following a 4-month period of bed rest in 3 healthy Soviet volunteers, Vico et al. found a two-fold increase in resorption surfaces, no increase in cell number, and reduced bone formation rate in specimens from the iliac crest (21). A puzzling observation was no measurable change in the volume of bone in healthy bed rest subjects, unlike patients with paraplegia (11). That the normal subject shows changes in surface morphology indicative of bone loss with no apparent diminution in volume at the two-dimensional level, suggests some form of compensation in microarchitecture. Either standard measurements may not be sensitive enough to detect losses in volume or other measurements involving the three-dimensional structure of bone, not usually done, may be needed to show how normal subjects maintain bone volume.

Gravity-Dependent Gradients of Mineralization

Comparison of the increments in whole-body calcium of rats exposed to 0, 1, and 2 g reveals accumulation of bone mineral directly related to the gravitational force (15). The mechanism of this acquisition of skeletal mineral must involve systemic as well as local processes. The cardiovascular system, whose general structure is oriented in the direction of gravity and where blood vessels, flow, and volume are known to differ at the local bone level in active and inactive individuals, is the most obvious candidate to influence bone mass.

Until recently, however, there were no data that suggested that there was a generalized cardiovascular effect on bone or that a shift of the hydrostatic column of pressure with changes in position, was associated with changes in bone mineral. In the tail-suspended rat, Roer and Dillaman found the expected decrease in ash in the bones of the unloaded lower extremities, no change in the humerus and ulna, and

importantly, an increase in bone ash in the skull (17). By dual photon absorptiometry, the density of the head region of adult bed rest subjects was found to be increased an average of 10% after a 30-day HDT study (1). These two studies suggest a gravity-dependent distribution of mineral in the whole skeleton, which may be a function of changing pressures, fluid flow, or volume in the cardiovascular system in response to change in position.

During the Cosmos 936 mission, centrifugation in orbit permitted comparison of the effects of gravity on the strength and growth of the femur of young rats in space (19). Rats treated with artificial gravity showed the same increases in density and strength during the 18.5-day flight as ground controls; however, the growth defect was not improved. Spengler et al. attributed the growth deficit to poor adaptation of the rats to the short-arm radius centrifuge and concluded that centrifugation normalized material properties, i.e., quality, but not the quantity of the femur. These paradoxical findings following artificial gravity could be explained by the recently observed linear gradients of mineralization in the diaphysis of the femur (10). At 1 g bone mineral concentration was lower in the distal than in the proximal diaphysis of the femur of the 14-week old rat, a disparity that persists in flight, but tends to disappear by 16 weeks on Earth. Because of the logistical problems connected with the 1887 flight where these diaphyseal gradients of mineralization were observed, and because the results differ from our expectation that mineral deposition proceeds from the center of a growing bone proximally and distally, confirmation of this observation is needed. Collectively, all of the above studies reveal an important connecting link between gravity, per se, and bone mineral distribution and deposition, most likely related to the cardiovascular system. The interaction of what appear to be gravity-dependent gradients visible at the whole-body and organ level, with the highly regulated processes that change bone structure at the local tissue level in response to biomechanical forces is not now apparent.

In summary: Advances in recent years have enabled us to recognize that two principal components of calcium metabolism, the calcium endocrine system and bone, respond promptly (within days), to changes in body position and weightlessness. The vitamin D hormone may be the best candidate for mobilizing bone mineral early, and newly identified gravity-dependent gradients, probably involving the cardiovascular system, may have a significant role in its distribution at the whole-body level. These observations have given us a new perspective on the results of balance studies in healthy subjects and astronauts (18,22). During inactivity or weightlessness, negative balances in bone minerals may be more directly a reflection of diets, and alterations in the function of the gastrointestinal tract and kidney that parallel, but do not necessarily derive from the highly localized activities concerned with the restructuring of bone and redistribution of bone mineral to meet new functional requirements. These studies imply that bone biomechanics are more severely affected by spaceflight than bone mass.

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Orthostatic Hypotension

C. GUNNAR BLOMQVIST

Orthostatic hypotension is a common and sometimes disabling condition. Likely causes include many different defects that singly or in combination affect major mechanisms controlling blood flow, vascular resistance, arterial pressure, and intravascular volume. The control systems are complex, and their interactions are poorly understood. As a consequence, obvious and straightforward therapeutic approaches sometimes prove ineffective, but seemingly paradoxic measures are often helpful. These characteristics combine to make orthostatic hypotension a challenging topic.

CAUSES OF RECURRENT EPISODIC ARTERIAL HYPOTENSION

Syncope is a common manifestation of orthostatic hypotension. The principal mechanism of syncope, including the orthostatic variety, is a transient reduction in cerebral blood flow. Causes of recurrent episodes of arterial hypotension include cardiac *dysrhythmias*. Bradyarrhythmias, tachyarrhythmias, and intermittent atrioventricular conduction blocks can cause reductions in cardiac output of sufficient magnitude to impair cerebral perfusion, particularly in patients with coexisting cerebrovascular disease. *Mechanical obstruction* of systemic or pulmonary blood flow may produce global cerebral ischemia with syncope. Such conditions include valvular aortic or pulmonary stenosis, idiopathic hypertrophic subaortic stenosis, atrial myxoma, and pulmonary embolic or vascular disease with pulmonary hypertension.

A wide range of emotional and somatic afferent stimuli can precipitate *vasodepressor* or *vasovagal syncope*. Neither term is strictly accurate. The cardiovascular response usually includes both bradycardia and vasodilatation, and impulse flow is altered in both the parasympathetic and sympathetic portions of the autonomic nervous system. The typical psychological circumstances involve a perception of an actual or symbolic injury that the victim feels that he or she should be able to face without fear. Obligations to submit to painful or unfamiliar diagnostic or therapeutic procedures are prime examples.[1] Among the somatic mechanisms are carotid sinus hypersensitivity[2] and abnormal impact of afferent impulses from the ear, mouth, larynx, and pharynx (*e.g.*, in glossopharyngeal neuralgia).[3] Simple swallowing (deglutition syncope)[4] may precipitate vasodepressor syncope in some persons. The hemodynamic events have been well documented.[1,5–7] A typical sequence includes an initial phase with moderate tachycardia followed by a marked fall in heart rate and arterial pressure. The depressor phase of the response has many features in common with orthostatic hypotension that progresses to syncope and later will be discussed in some detail.

PATHOPHYSIOLOGY OF ORTHOSTATIC HYPOTENSION

PRINCIPAL FEATURES

Orthostatic or postural hypotension may be defined as the inability to maintain adequate arterial pressure and tissue perfusion in the upright position. The brain is almost always the organ most vulnerable to postural hemodynamic changes, but orthostatic angina pectoris has been described.[8] Syncope is the manifestation of grossly inadequate cerebral blood flow. Lesser degrees of hypoperfusion cause vague weakness and postural dizziness or faintness. Many different clinical conditions are associated with orthostatic intolerance. Some patients have severe and widespread structural neurologic and cardiovascular abnormalities. Others appear to have strictly functional disorders.

Two major mechanisms cause orthostatic intolerance: (1) relative central hypovolemia with postural decreases in cardiac filling and stroke volume to subnormal levels and (2) inadequate regulatory responses to the decrease in stroke volume and cardiac output.

The conventional terminology in this area is often inappropriate and confusing because it is based exclusively on the responses mediated by the sympathetic nervous system. It would be preferable to use dual descriptors referring to changes in intravascular volume and to regulatory responses. "Sympaticotonic orthostatic hypotension" may then be characterized as hypovolemic hyperreactive orthostatic hypotension. The "asympaticotonic" variety would be referred to as normovolemic hyporeactive orthostatic hypotension.

GRAVITY, CARDIOVASCULAR PRESSURE–VOLUME RELATIONSHIPS, AND STARLING'S LAW

All intravascular pressures have a gravity-dependent hydrostatic component (Fig. 1).[9,10] The interactions between the gravitational field, the position of the body, and the structural and functional characteristics of the blood vessels determine the distribution of intravascular volume. This, in turn, has major effects on cardiac filling and pump function.

Data on human blood volume, its distribution, and vascular pressure–volume relationships have been reviewed by Blomqvist and Stone.[10] Total blood volume in mammals is a linear function of body weight. Mean values in normal adult humans cluster around 75

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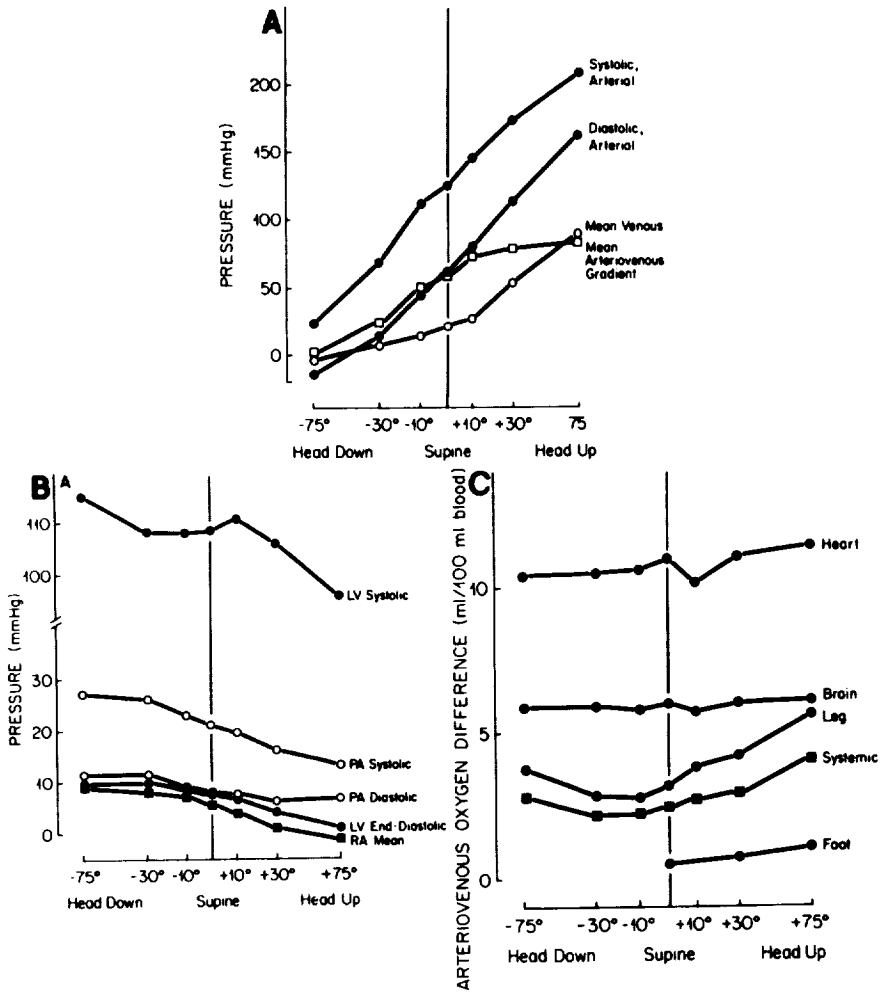

Fig. 1. Responses to graded head-up tilt in ten young normal men. Intravascular pressures in foot (**A**) and in central circulation (**B**). Arteriovenous oxygen difference (**C**). Angle of tilt (horizontal axis) plotted as sine function to provide linear scale for primary hydrostatic effects of body-position changes, based on data from Katkov and Chestukhin.[9] (*LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium) (Blomqvist CG, Stone HL: Cardiovascular adjustments to gravitational stress. In Shepherd JT, Abboud FM (eds): Handbook of Physiology, Section 2, The Cardiovascular System. Volume III: Peripheral Circulation and Organ Blood Flow, Part 2, pp 1025–1063. Bethesda, MD, American Physiological Society, 1983)

ml/kg, corresponding to a total of 5 to 5.5 liters in a 70-kg person. High levels of physical activity and adaptation to a hot climate cause expansion of the blood volume with balanced increases in red blood cell mass and plasma volume.

Approximately 70% of the total blood volume is contained in the systemic veins; the heart and the lungs account for 15%, the systemic arteries for 10%, and the capillaries for 5%. Effective total vascular compliance represents the summed compliances of the various vascular compartments. It is dominated by the systemic veins. Measurements are derived by monitoring central venous pressure during acute changes in blood volume. Normal human compliance values are of the order of 2 to 3 ml/mm Hg/kg. Effective compliance is an empiric measurement, complicated by reflex hemodynamic adjustments with secondary redistribution of venous volume, by delayed compliance (viscoelastic creep of the vessel walls), and by adjustments in plasma volume by tissue filtration. Nevertheless, it provides a useful measure of the impact on right-sided cardiac filling pressures of acute hypovolemia and hypervolemia.

A simple Frank-Starling relationship (stroke volume as a function of end-diastolic volume or pressure) is a reasonably accurate descriptor of cardiac performance during postural changes in healthy persons at rest. There are normally no major changes in arterial blood pressure. Afterload, expressed as end-systolic wall stress, is usually slightly reduced in the upright position. The normal left ventricle ejects more than half of its end-diastolic volume, usually between two thirds and three fourths (Table 1).[11,12]

Stroke volume varies in direct proportion to changes in end-diastolic volume (Fig. 2).[13] Increases in ejection fraction with secondary increases in stroke volume, mediated by positive inotropism, are of only minor functional significance during acute interventions that primarily affect ventricular filling. Arterial pressure is maintained by adjustments in heart rate and systemic vascular resistance.

CEREBRAL PERFUSION

Cerebral blood flow is normally tightly controlled by autoregulation. It remains stable over a wide range of mean arterial pressure at normal levels of arterial carbon dioxide partial pressure. Cerebral blood flow usually starts to decrease significantly when driving pressure (mean arterial pressure at the eye level) falls

TABLE 1. Postural Cardiovascular Adjustments in Normal Human Subjects

Parameter	Supine	Sitting	*p*
Left ventricular volume (ml)*			
End-diastolic	107 ± 10	85 ± 6	<0.02
Endsystolic	34 ± 4	32 ± 5	
Stroke	76 ± 8	55 ± 5	<0.05
Ejection fraction (%)	76 ± 2	72 ± 4	
Heart rate (beats per minute)†	73 ± 4	84 ± 4	<0.001
Pressure (mm Hg)			
Brachial artery	96 ± 3	99 ± 4	
Systolic	130 ± 5	132 ± 5	
Diastolic	76 ± 3	82 ± 3	<0.05
Pulmonary artery	13 ± 1	13 ± 1	
Pulmonary capillary wedge	6 ± 1	4 ± 1	<0.001
Left ventricular end-diastolic	8 ± 1	4 ± 1	<0.001
Stroke index (ml/m^2)	50 ± 5	35 ± 3	<0.001
Cardiac index (liters/min/m^2)	3.5 ± 0.3	2.8 ± 0.2	<0.001

* Left ventricular scintigraphic data (mean ± standard error) from seven young normal subjects studied by Poliner and co-workers.[11]
† Hemodynamic measurements from ten sedentary men, aged 32 to 58 examined by Thadani and Parker.[12]

below 50 mm Hg. Consciousness may be lost when blood flow falls below one fourth of normal, which usually occurs at a mean pressure of about 40 mm Hg.[14] The hydrostatic gradient between the levels of the heart and the brain in the upright position adds 30 mm Hg to the required pressure as measured at the heart level. A mean arterial threshold pressure of 70 mm Hg corresponds to systolic and diastolic pressures of about 80/65 mm Hg. A significant shift of the autoregulatory range to the left is likely to occur in chronic autonomic dysfunction[15] with orthostatic hypotension, and a right-ward shift is a feature of systemic hypertension.

NORMAL RESPONSES TO ORTHOSTATIC STRESS

A change in body position from supine to standing or sitting initiates a well-defined sequence of events[10,16,17]:

1. Blood volume is redistributed away from the heart. About 500 ml is removed from the intrathoracic region to the legs. An additional volume of 200 to 300 ml is transferred to the veins in the buttocks and the pelvic area.
2. Cardiac filling pressures fall, and stroke volume decreases, usually by 20% to 30%.
3. An equally large acute decrease in arterial pressure is prevented by rapid baroreflex-induced increases in heart rate and systemic vascular resistance. Additional neurohumoral mechanisms are activated within minutes to preserve adequate intravascular volume and to help maintain arterial pressure.
4. Cerebral perfusion pressure is kept within the autoregulatory range.

The principal features of the human cardiovascular response to orthostatic stress are shown in Figure 3.

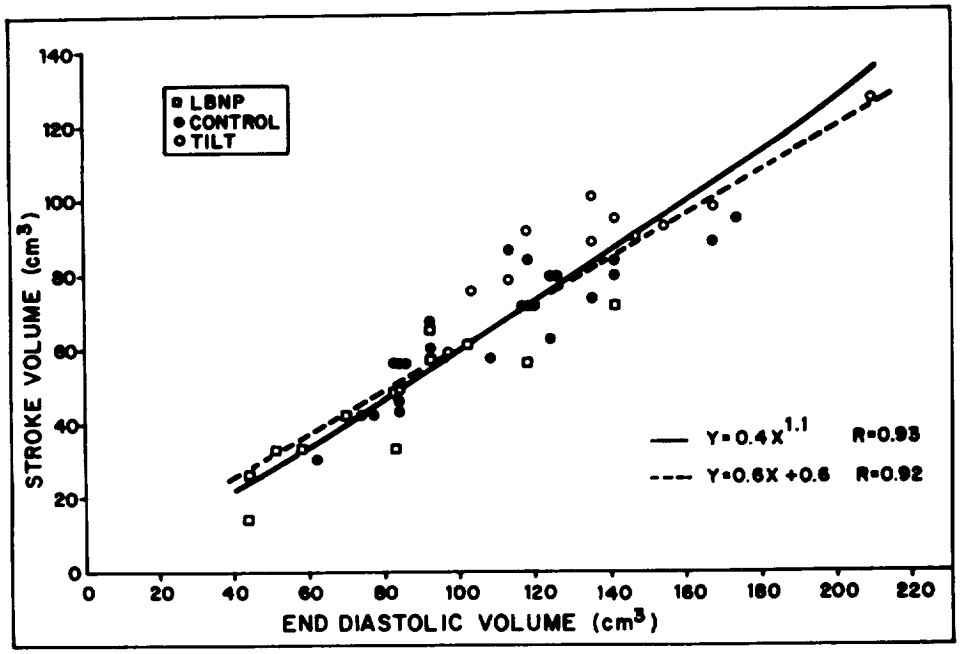

Fig. 2. Relationship between left ventricular stroke volume and end-diastolic volume. Echocardiographic measurements in 12 normal young men. Large variations in preload were introduced by head-down tilt at 5° and lower body negative pressure (LBNP) at −40 mm Hg. (Nixon JV, Murray RG, Leonard PP et al: Effects of large variations in preload on left ventricular characteristics in normal subjects. Circulation 65:698–703, 1982) By permission of the American Heart Association, Inc.

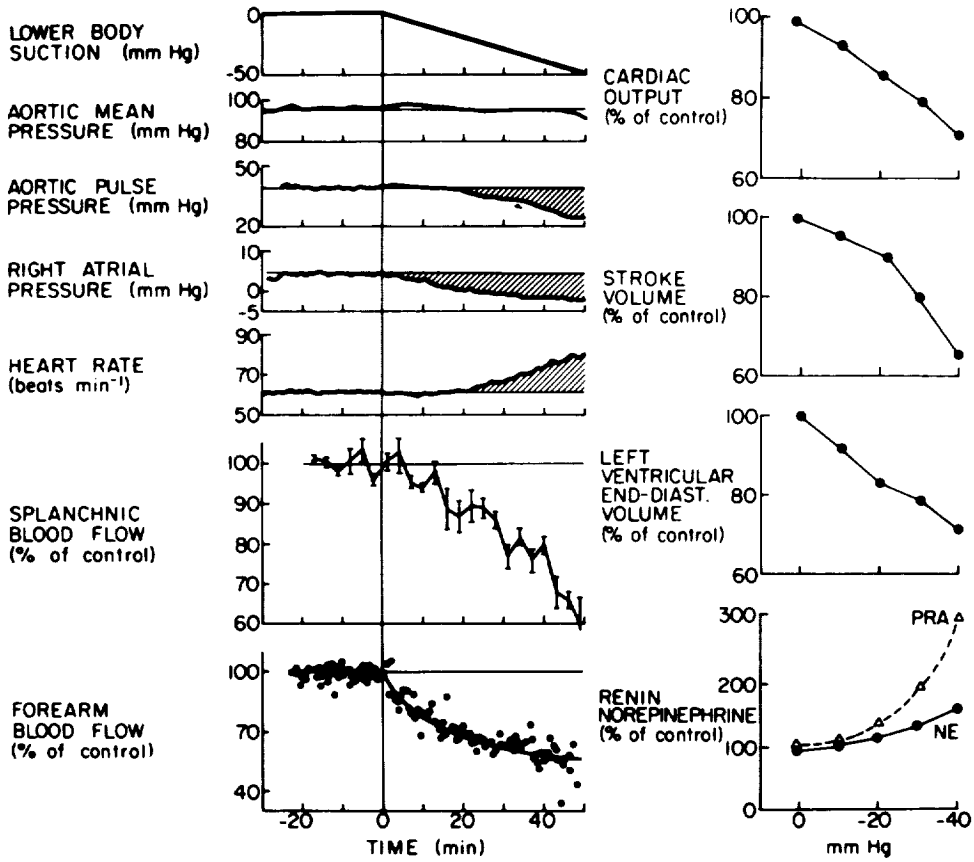

Fig. 3. Cardiovascular responses to graded lower body negative pressure. Panels on the left show average responses to suction applied at a continuous rate of −1 mm Hg min^{-1} for 50 minutes.[18] Panels on the right show central circulatory responses to 10-mm Hg steps in negative pressure down to −40 mm Hg.[19] (Rowell LB: Human Circulation: Regulation During Physical Stress, pp 137–173. New York, Oxford University Press, 1986)

The data represented in the figure were collected during lower body negative pressure (LBNP). Application of LBNP produces a redistribution of intravascular volume similar to that which occurs during a transition from supine to sitting or standing. The use of LBNP facilitates many measurements. LBNP also gives the experimenter better control of the stimulus by minimizing skeletal muscle activity that has major effects on the blood volume distribution and on the dynamic cardiovascular response. Furthermore, in the microgravity environment of space, LBNP provides a means of studying the equivalent of gravitational postural shifts of intravascular volume.

Figure 3 shows a progressive decrease in right atrial pressure, left ventricular end-diastolic volume, stroke volume, and cardiac output. Aortic pressure during the early stages is maintained by vasoconstriction only. Initially this involves the skin and skeletal muscle (forearm), but later the splanchnic region is also involved. Further decreases in stroke volume are partially offset by increasing heart rate. Plasma levels of norepinephrine increase, representing overflow from vascular receptors, and plasma renin activity levels are also elevated in response to large decreases in cardiac filling.[17–19]

TOTAL BLOOD VOLUME AND MECHANISMS CONTROLLING ITS DISTRIBUTION

Variations in total blood volume well within the physiological range may affect orthostatic tolerance.[20,21] The relative degree of peripheral pooling is also important. Patients with massive venous varicosities or a congenital absence of the venous valves have postural hypotension and decreased exercise capacity in the upright position.[22] Ambient temperature also affects the degree of peripheral pooling, probably mainly by altering skeletal muscle tone. Heat markedly reduces, and cold increases, orthostatic tolerance.[23] Relative rather than absolute magnitude determines the hemodynamic impact of peripheral redistribution of blood. Subsets of patients (*e.g.*, those with mitral valve prolapse syndrome) with orthostatic hypotension and reduced total blood volume may pool no more or even less than normal controls in terms of absolute volume.[24] Other patients with intact autonomic function have a combination of increased absolute peripheral venous pooling and reduced total blood volume.[25]

Considerable controversy exists regarding the extent to which active reflex-mediated venomotor changes contribute to cardiovascular homeostasis during

changes in posture.[17,26,27] In general, active venoconstriction may occur in the skin and in the splanchnic region. Veins supplying skeletal muscle are poorly innervated, and plasma concentrations of norepinephrine rarely reach levels that would produce venoconstriction. Furthermore, the deep veins in the leg have very thin walls. Venous compliance is largely determined by the characteristics of skeletal muscle. Mayerson and Burch measured intramuscular pressures in young persons who had had multiple episodes of orthostatic hypotension progressing to syncope.[28] Fainters had lower intramuscular pressures in the leg at rest and subnormal pressure increases during head-up tilt. Buckey and associates used a combination of magnetic resonance imaging (MRI) and occlusion plethysmography to examine the capacity of the deep leg veins.[29] At distending pressures equivalent to the hydrostatic venous pressures in the upright position, more than one half of the increase in leg volume was accommodated by the deep veins (Fig. 4). This finding implies that the properties of skeletal muscle are likely to affect significantly the distribution of venous volume and cardiac filling also at rest when the muscle pump is inactive.

Local reflex mechanisms may contribute to the vascular response to orthostatic stress. In experimental animals, activation of venous afferent fibers by distention produces reflex-induced leg muscle activity that may counteract postural pooling.[30,31] However, attempts to demonstrate a similar reflex in humans performed by Blomqvist and associates have been unsuccessful. Vasoconstriction with decreased limb blood flow in response to local venous distention mediated by a local (axonal) sympathetic reflex mechanism has been demonstrated by Henriksen and Sejrsen.[32,33]

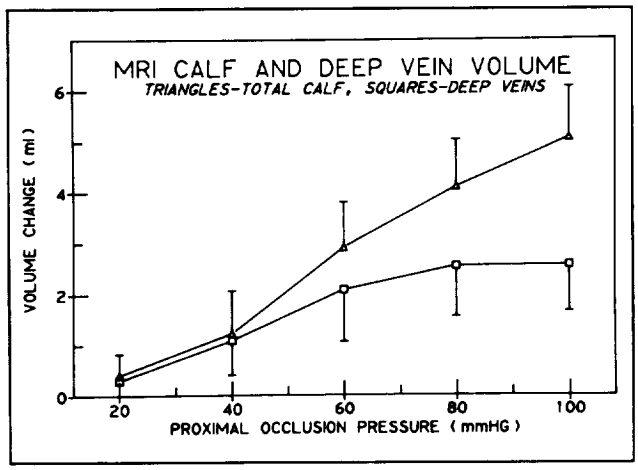

Fig. 4. Changes in deep venous volume and total leg volume with increasing venous occlusion pressures. Measurements derived by quantitative analysis of cross-sectional magnetic resonance images of the lower leg. (Buckey JC, Peshock RM, Blomqvist CG: Deep venous contribution to hydrostatic blood volume change in the leg. Am J Cardiol 62:449–453, 1988)

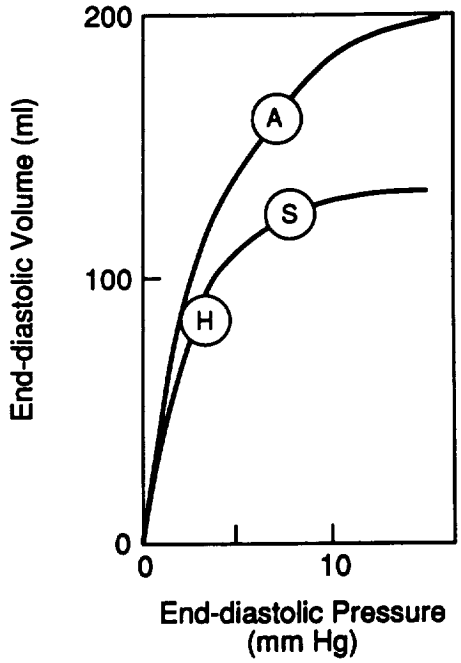

Fig. 5. Potential mechanisms by which the diastolic pressure–volume characteristics of the normal left ventricle may affect orthostatic tolerance. In the supine position, sedentary subjects (*S*) operate at near-maximal volume, that is, on the relatively flat portion of the curve. Hypovolemia with a decrease in filling pressure (*H*) will cause a shift toward the steep portion and potentiates the effects on ventricular volume of further decreases in filling pressure. There is suggestive evidence that endurance athletes (who usually have large diastolic volumes) normally operate on the steep portion of the function curve (*A*). This provides a mechanism augmenting end-diastolic volume and stroke volume when filling pressures increase during exercise. However, there will also be a large orthostatic decrease in stroke volume that may help explain why high levels of aerobic fitness sometimes are associated with orthostatic hypotension. (Based in part, on data from Parmley WW: Ventricular function. In Parmley WW, Chatterjee K (eds): Cardiology, vol 1, chap 5. Philadelphia, JB Lippincott, 1988)

CARDIAC PRESSURE-VOLUME CHARACTERISTICS

Cardiac pressure-volume characteristics during diastole (Fig. 5) are likely to modulate the systemic effects of any given decrease in intrathoracic blood volume. In the supine position in normal sedentary subjects, the left ventricle appears to be operating close to its maximal functional diastolic volume. Increases in filling pressure during exercise or intravenous fluid loading, or during the two interventions combined, produce only minor increases in end-diastolic volume and stroke volume.[10,34,35]

Hypovolemia decreases orthostatic tolerance for several different reasons. Large losses of intravascular volume lower supine filling pressure, end-diastolic volume, and stroke volume and magnify the orthostatic decreases in ventricular filling and stroke volume. Any absolute amount of postural venous pooling will represent a larger relative peripheral transfer in the hypovolemic subject. More importantly, hypovolemia alters the effective ventricular diastolic pressure–volume characteristics. The normal pressure–volume curve is nonlinear with a larger change in volume for any change in pressure at low filling pressures.[36] Hypovolemia causes a leftward displacement of the operating

point away from the flat portion of the function curve (where moderate increases and decreases in filling pressure have little effect on end-diastolic volume and stroke volume) toward the steep portion of the curve where any further reduction in filling pressure will cause a large decrease in stroke volume.

NEUROHUMORAL REGULATION

Short-term regulation of arterial blood pressure is accomplished mainly by neural mechanisms. Carotid, aortic, and cardiopulmonary mechanoreceptors are involved. These receptors all respond to deformation, that is, to stretch or compression caused by increased intracavitary or transmural pressures. Cardiopulmonary receptor densities are particularly high at the left-sided atriovenous junctions and in the inferoposterior portion of the left ventricular wall. Afferent impulses travel with the vagus and the glossopharyngeal nerves. The nucleus of the tractus solitarius is the primary site of interaction between impulse traffic in the baroceptor pathways and activity within the central nervous system.[37] Efferent fibers reach the sinus and atrioventricular nodes, the cardiac ventricles, and the systemic arterioles and veins by vagal and spinal cord pathways.

A fall in intravascular or intracardiac pressure decreases afferent impulse traffic. This releases central inhibitory activity and alters the efferent impulse flow. Parasympathetic drive decreases, but α- and β-adrenergic activities increase. Responses of the target organs include increased heart rate, increased contractility, and vasoconstriction with reduced blood flow to the skin, to inactive skeletal muscle, and to the renal and splanchnic regions. The majority of the β-receptors innervated by the sympathetic nerves are of the β_1 subtype. They regulate heart rate, cardiac contractile state, and release of renin from juxtaglomerular cells. The β_2-receptors of the resistance vessels in skeletal muscle have a vasodilator function but are not innervated.[38]

The existence of a triplicate system for neural control of blood pressure is well established,[39,40–42] but the interactions and degree of functional overlap between the three principal baroreflexes (carotid, aortic, and cardiopulmonary) are still poorly understood. Data from experiments in nonhuman species are not necessarily applicable to human physiology and medicine. Distributions of hydrostatic gradients and regional blood volume are markedly different in humans and quadrupeds, but interesting, minimally invasive and safe techniques have been developed for human use in the study of specific aspects of short-term reflex regulation of arterial pressure.

DIRECT MICRONEUROGRAPHIC STUDIES OF MUSCLE SYMPATHETIC NERVE ACTIVITY

A microneurographic technique for direct recording of human sympathetic nerve activity has been developed by Hagbarth and Vallbo[43] and has been applied extensively to the study of cardiovascular physiology by Wallin[44–46] and others.[47–51] The peroneal and median nerve are relatively easily accessible. A thin tungsten electrode is inserted into a nerve fascicle supplying either muscle or skin. An impulse pattern with pulse-synchronous bursts in response to changes in blood pressure identifies a muscle nerve supplying vascular terminals (Fig. 6). Quantitation of the impulse traffic provides a direct measure of efferent vasoconstrictor activity. The time resolution is excellent, and measurements are highly reproducible in a given subject.

CAROTID AND AORTIC BAROCEPTORS

More than 30 years ago, two British flight surgeons, Ernsting and Parry, described an ingenious noninvasive technique to test carotid baroceptor function.[52] Suction applied to the neck area by means of an airtight collar produces an increase in transmural arterial pressure and increased deformation of the mechano-

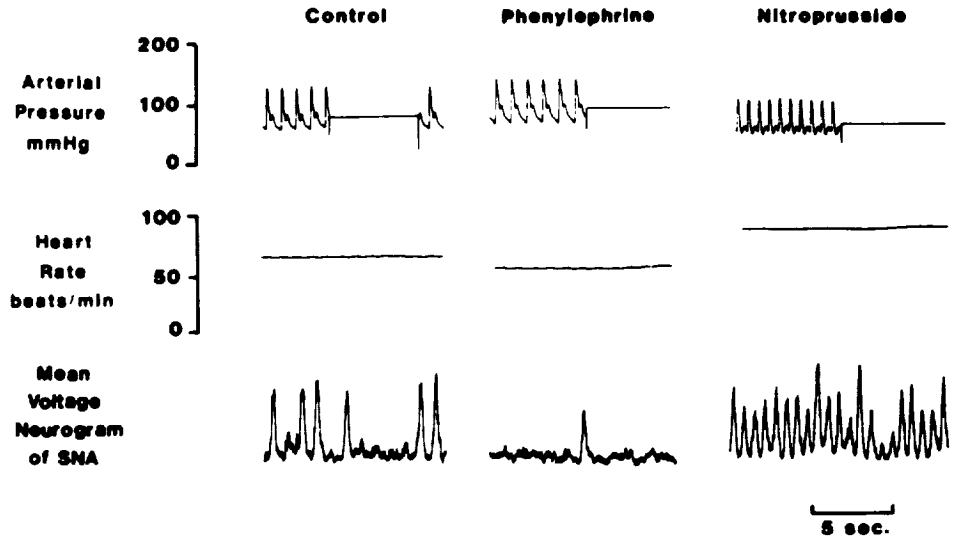

Fig. 6. Arterial baroreceptor reflex responses: effect of elevating phasic and mean arterial pressure with phenylephrine and lowering pressure with nitroprusside on heart rate and efferent muscle sympathetic nerve activity (SNA) in a normal subject. SNA is pulse synchronous. An 8-mm Hg increase in arterial pressure (phenylephrine) caused marked reflex inhibition of SNA and a reflex fall in heart rate. A 15-mm Hg fall in arterial pressure (nitroprusside) caused an increase in SNA and heart rate. (Aksamit TR, Floras JS, Victor RG et al: Paroxysmal hypertension due to sinoaortic baroceptor denervation in humans. Hypertension 9:309–314, 1987)

ceptors. The stimulus closely simulates an increase in intravascular carotid pressure, but there are no significant direct hemodynamic effects.

The approach has been refined and used extensively by Eckberg and his associates to evaluate the vagally mediated effects on heart rate.[53-57] A computer-controlled system delivers an electrocardiogram-triggered ramp of neck collar pressures. Each pressure level is imposed only during a single cardiac cycle. The reflex response time is very short. The effect of a change in transmural pressure is measured during the next cardiac cycle. The pressure ramp is easily repeated and stimulus–response curves (Fig. 7) can be based on multiple measurements. Characteristic abnormalities have been described in hypertension.[55] The operating point is reset in mild disease, and the sensitivity or slope is reduced in more advanced cases.

Major assets of this approach are the lack of effect on the native hemodynamic state and the relative ease by which complex quantitative data can be acquired. On the other hand, the procedure generates data only on the heart rate component of the reflex. Activation of the carotid baroceptors by increased transmural pressure of longer duration also affects the sympathetic nerve traffic to the resistance vessels in skeletal muscle.[51] At least theoretically, carotid baroceptor function may be normal in the presence of attenuated heart rate responses if the vasomotor effects are enhanced.

The operating characteristics of the carotid and aortic baroreflexes appear to be different in different species. In dogs, the aortic reflex has a higher threshold and lower sensitivity than the carotid baroreflex. Ferguson and associates[58] and Sanders and co-workers[59] used a combination of the direct sympathetic nerve recording technique and the pressurized neck collar to examine the relationship between aortic and carotid reflexes in human subjects. Phenylephrine was infused with and without external pressure application to the neck to cancel the effects on transmural carotid sinus pressure. This approach left the aortic baroceptors free to respond. The carotid baroceptors were also activated separately by neck suction. The results confirm that both reflexes participate in the control of arterial pressure in human subjects and suggest that the aortic reflex is more powerful than the carotid. The greater sensitivity applies to the control of both heart rate and adrenergic vasoconstrictor activity.

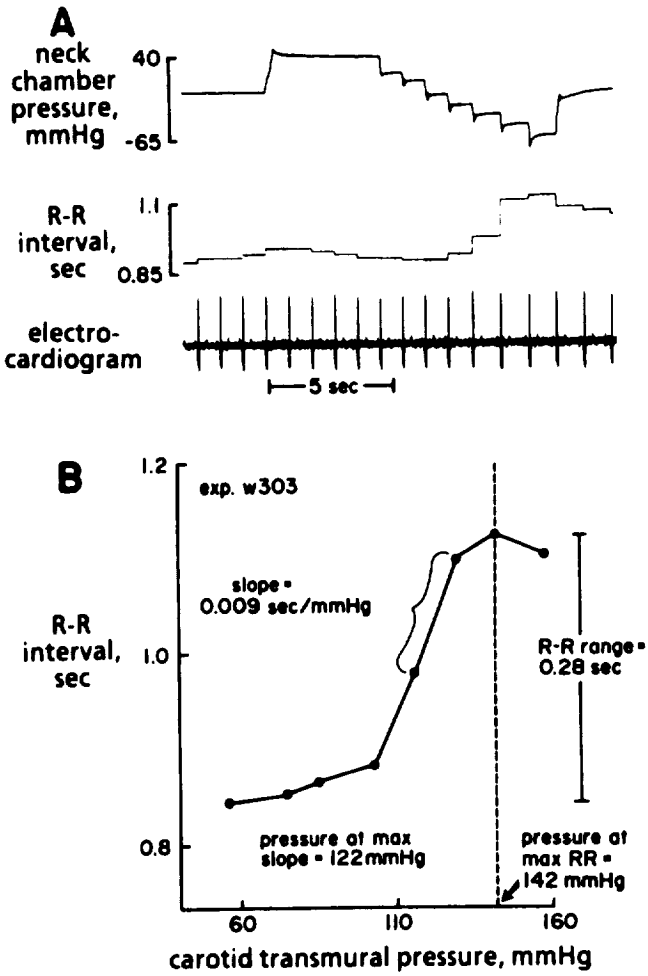

Fig. 7. Experimental record (A) and average responses of one subject to seven applications of neck pressure sequence (B). B indicates method used to analyze baroreflex relations. Carotid transmural pressure was considered to be average systolic pressure minus neck chamber pressure. Pressure at maximum slope was taken as carotid transmural pressure halfway between pressures bracketing maximum slope. (Kasting GA, Eckberg DL, Fritsch JM et al: Continuous resetting of the human carotid baroreceptor–cardiac reflex. Am J Physiol 252 (Regulatory Integrative Comp Physiol 21): R732–R736, 1987)

LOSS OF ARTERIAL BAROCEPTOR FUNCTION

Aksamit and colleagues described a patient with loss of carotid and aortic baroceptor function attributable to a combination of surgery and radiation therapy.[48] Large changes in arterial pressure, induced by infusions of phenylephrine and nitroprusside, failed to affect heart rate or directly measured adrenergic vasomotor nerve activity. The patient had retained cardiopulmonary reflex activity and responded to an LBNP-induced decrease in cardiac filling with a marked increase in sympathetic nerve activity. Arterial pressure was labile, but sustained hypertension was not present. Sinoaortic denervation in experimental animals produces a similar state. Thus, cardiopulmonary baroceptors may contribute to the control of arterial pressure, but are by themselves unable to prevent rapid changes in arterial pressure. The patient was mildly orthostatic.

CARDIOPULMONARY RECEPTORS

The principal components of the cardiopulmonary receptor system are the left atrial and left ventricular receptors. Both sets respond to deformation. The atrial receptor population directly monitors atrial filling and indirectly monitors ventricular filling. The ventricular receptors discharge primarily during systole, but are also influenced by diastolic events. Changes in ventricular wall stress, which is maximal during isovolumic systole, may be the primary stimulus.

There are numerous and complex interactions between the mechanisms maintaining arterial pressure and body fluid homeostasis. Arterial pressure levels directly affect tissue filtration rates and renal excretion of sodium and water. The arterial and cardiopulmonary baroreflexes also control renal sympathetic activity (α-adrenergic vasoconstriction, β_1-mediated activation of the renin–angiotensin system). Vasopressin (antidiuretic hormone) is released from the neurohypophysis in response to increases in plasma osmolarity as detected by receptors in the hypothalamus. Vasopressin is also released when the atrial mechanoreceptors are unloaded by decreasing filling pressures, usually as a consequence of decreased central blood volume. Unloading of ventricular and arterial baroceptors by decreases in transmural pressures also releases vasopressin. The relative importance of these receptor sites is not known in detail, but the atrial release mechanism may be less active in primates than in other species. Vasopressin may be physiologically important as a vasoactive substance, inducing vasoconstriction in skeletal muscle and the splanchnic area and vasodilatation in the coronary and cerebral circulations by a combination of endothelium-dependent (cyclo-oxygenase-mediated, indomethacin-inhibited) and direct relaxation of smooth muscle.

Release of atrial natriuretic peptide (ANP) is caused by an increase in atrial transmural pressures. In addition to inducing natriuresis, ANP has multiple effects including vasodilatation and venodilatation, inhibition of renin and vasopressin release, and perhaps also a direct effect on capillary permeability.[17,38,60]

LBNP at nonhypotensive levels has been used as a means of unloading the low-pressure cardiopulmonary receptors without affecting the arterial sensors. LBNP in the range −5 to −10 or −15 mm Hg produces significant vasoconstriction, but there is no change in arterial systolic or diastolic pressures. Pulse pressure and aortic pulse contour also remain unchanged at moderate LBNP levels. These findings, combined with the absence of any heart rate change (see Fig. 3 and Rowell[17]), provide evidence for preferential involvement of the low-pressure receptor pathway and suggest that the principal response is vasoconstriction. However, cardiac filling pressures and stroke volume decrease. This is likely to cause a decrease in aortic and arterial pulse volume with a significant secondary change in carotid sinus and aortic wall stress. Some degree of activation of arterial baroreflexes cannot be ruled out, and the ventricular receptors may also respond.

LOSS OF CARDIOPULMONARY RECEPTOR FUNCTION

Current surgical technique in cardiac transplantation preserves the dorsal portion of the atria, including the neural pathways to and from the left atrial receptors. The efferent pathways to the right atrium and the sinus node are also intact, but the node is electrically isolated from the transplanted heart. The ventricular baroceptors are, of course, lost. Mohanty and associates reported marked attenuation of the normal reflex-induced increases in forearm vascular resistance and plasma norepinephrine levels during LBNP after cardiac transplantation.[61] The impaired responses were not caused by treatment with immunosuppressive agents. Renal transplant patients on similar regimens had enhanced vasoconstrictor responses. Furthermore, the vasomotor and norepinephrine responses to a cold pressor test were intact in the cardiac transplant patients. The combined data suggested to the authors that the impaired vasoconstrictor responses were caused by ventricular denervation. However, the patients in this series tended to be hypertensive; post-transplant patients tend to be hypertensive (as a side effect of cyclosporin treatment) and their mean forearm vascular resistance at rest was higher than in control subjects during LBNP at −40 mm Hg. Mean arterial pressure during LBNP was equally well maintained in patients and controls.

Victor and colleagues studied 12 patients after cardiac transplantation and six normal controls.[50] Left ventricular dimensions during LBNP at −14 mm Hg decreased to the same extent in both groups. There was no change in mean arterial pressure or heart rate in the control group. Muscle sympathetic nerve activity (MSNA) during LBNP, measured directly with the microelectrode technique, was twice as high as at rest. Compared with normal controls, the transplant patients had higher MSNA at rest, but an identical relative change during LBNP. Sinus rate in the atrial remnant increased by 6 beats per minute in the patients, and mean arterial pressure fell by 3 mm Hg. The increases in MSNA and sinus node rate were abolished when mean arterial pressure was kept constant during LBNP by infusion of phenylephrine. These data indicate that arterial baroreflexes can compensate for loss of the ventricular receptor function.

INTERACTIONS BETWEEN ARTERIAL AND CARDIOPULMONARY BAROREFLEXES

Vasovagal or vasodepressor syncope and orthostatic syncope in subjects with intact autonomic nervous system have many common features.[1,5,6,39] There is an initial phase with moderate tachycardia and vasoconstriction, followed by a marked fall in heart rate and arterial pressure. There is little or no increase in plasma norepinephrine in response to the hypotension (Fig. 8). The cutaneous circulation is usually vasoconstricted, but there is a large decrease in systemic resistance caused by vasodilatation in skeletal muscle.[7] Paradoxic vasodilatation and bradycardia are also common features of hemorrhagic shock.[39,62] Data obtained by direct nerve recording techniques have documented a strong inhibition of impulse traffic in the α-adrenergic vasoconstrictor fibers supplying skeletal muscle during presyncope and syncope.[45,46]

The most likely cause of this sequence of events is conflicting inputs from arterial and cardiopulmonary

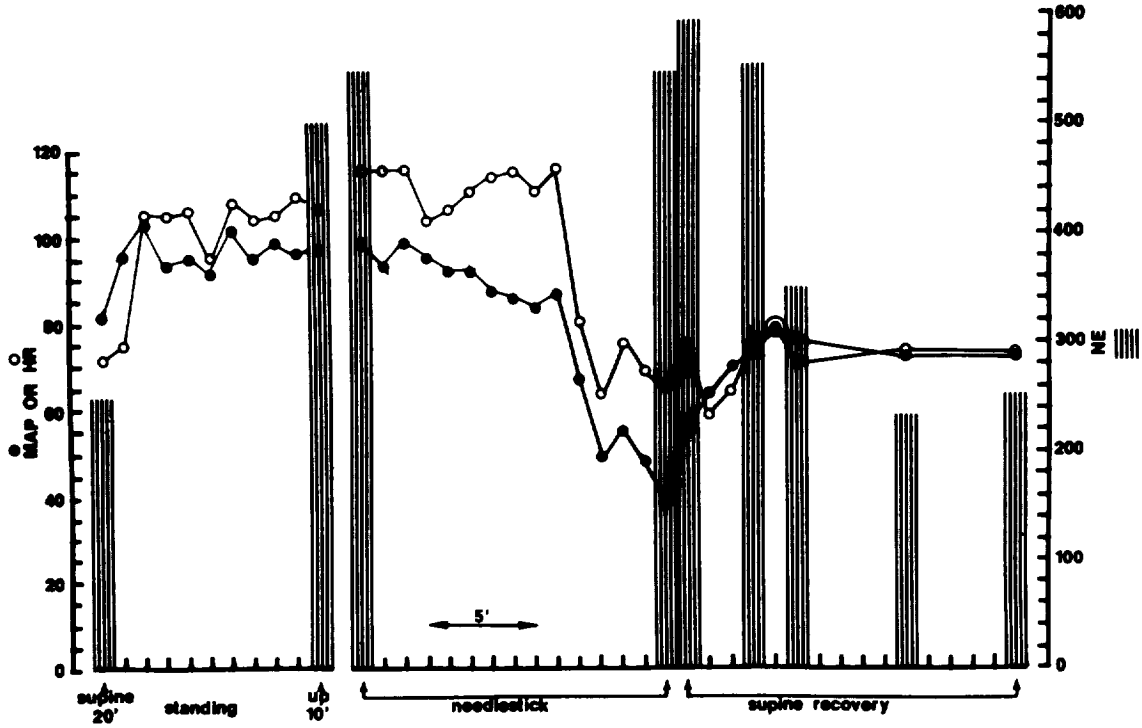

Fig. 8. Mean arterial pressure (*MAP*), heart rate (*HR*), and plasma norepinephrine (*NE*) concentrations during syncope evoked by the emotional response to insertion of an intravenous needle in a 17-year-old female patient who suffered from recurrent syncopal episodes. Syncope was associated with severe hypotension and bradycardia. There was no norepinephrine response to hypotension during syncope, although the norepinephrine response to standing was intact. (Goldstein DS, Spanarkel M, Pitterman A et al; Circulatory control mechanisms in vasodepressor syncope. Am Heart J 104:1071–1075, 1982)

baroreflexes. The left ventricular receptors are normally activated by increased intracavitary pressure and/or volume with increased wall stress. A progressive reduction in ventricular volume probably occurs during the presyncopal stage. Echocardiographic studies have demonstrated gradually decreasing left ventricular volumes with increasing degrees of peripheral venous pooling.[19] The left ventricular endocardial receptors will eventually be activated by direct compression. The salient stimulus is deformation, but the sensing system cannot differentiate between compression, which is associated with low volume and pressure, and distension, which is caused by high ventricular pressure and volume. The normal adjustments to reduced cardiac output and arterial pressure are negated, and bradycardia and vasodilatation are produced. An unstable autonomic state sometimes occurs during the presyncopal phase with large oscillations in heart rate and arterial pressure (Fig. 9).[63] This may reflect variations in the balance between opposing drives from ventricular and arterial receptors (*i.e.*, deformation of the ventricular receptors in an empty heart falsely signaling high left ventricular pressures at a time when the carotid and aortic receptors sense a low arterial pressure[16]) or represent an exaggeration of the intrinsic 0.1 Hz cyclical variations in adrenergic vasomotor activity.[64]

There is strong collateral support for an important role for the ventricular baroceptors. β-Adrenergic blockade increases left ventricular end-diastolic and endsystolic volumes and improves orthostatic tolerance after bed rest.[65] Activation of ventricular deformation receptors by high ventricular transmural pressure or direct contact is likely to be the principal cause of syncope in aortic stenosis and in idiopathic hypertrophic subaortic stenosis.[39] Bradycardia and arterial hypotension are also common features during the early stages of an acute inferior or inferoposterior myocardial infarction.[39] The activity of ventricular mechanoreceptors is likely to be enhanced by increased deformation of the ischemic segment of the ventricular wall. Reflex inhibition of renal sympathetic activity may, at least theoretically, limit the ability to conserve intravascular volume and to enhance vasoconstrictor responses (no renal vasoconstriction and no activation of the renin–angiotensin system). The hemodynamic effects at rest are usually transient, but relative bradycardia and hypotension are often present during the standard submaximal exercise test at discharge. The attenuated exercise responses are usually normalized within a few weeks when the healing process is completed (unpublished observations), and there is likely to be less deformation in or at the edge of the infarcted area.

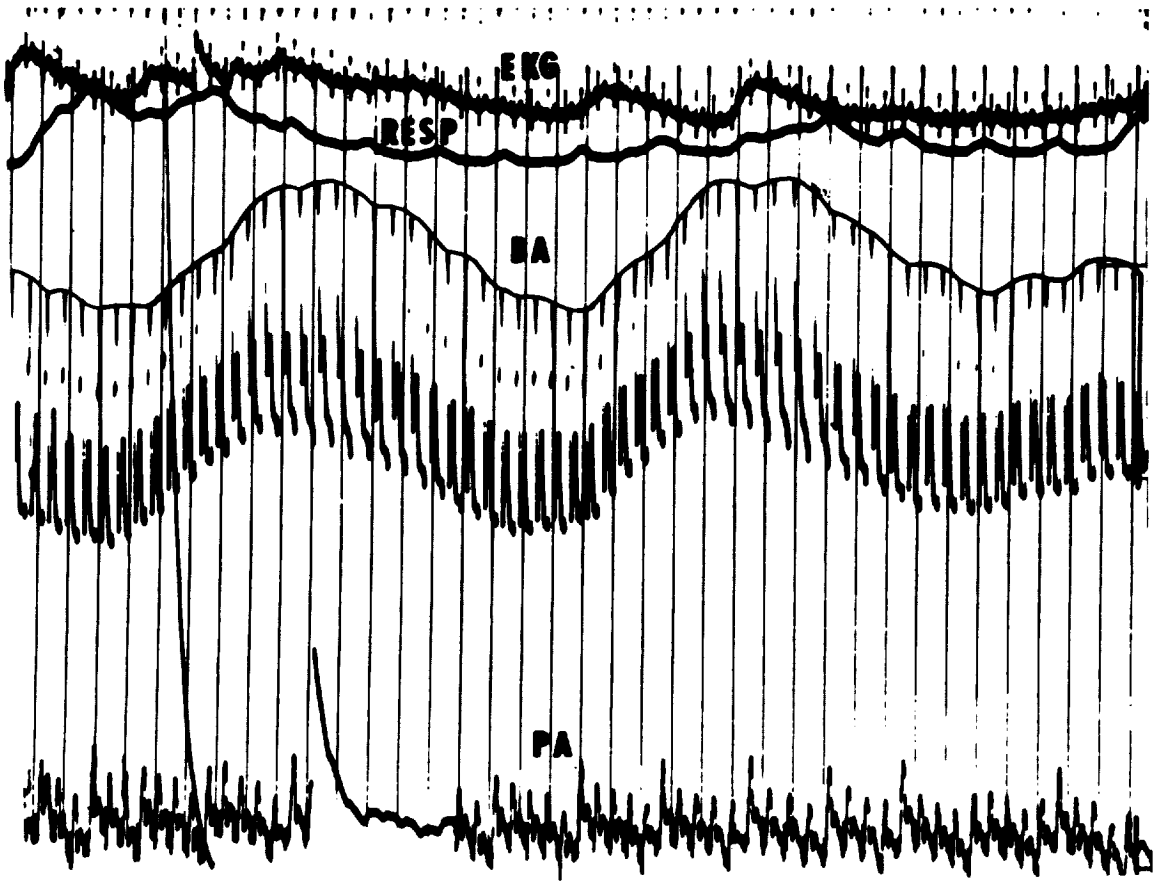

Fig. 9. Vasomotor waves are present in the brachial artery pressure tracing (*BA*) but are not seen in the pulmonary artery pressure tracing (*PA*). Waves are unrelated to respiration (*RESP*) and are now believed to represent variations in α-adrenergic activity. The periodicity usually approximates 0.1 Hz. These waves were recorded during 70° head-up tilt after a 14-day bed rest period in a subject with reduced orthostatic tolerance. (Hyatt KH: Hemodynamic and body fluid alterations induced by bed rest. In Murray RM, McCally M (eds): Hypogravic and Hypodynamic Environments, pp 187–209. Washington, DC, National Aeronautics and Space Administration, 1971)

CLINICAL ASPECTS OF ORTHOSTATIC HYPOTENSION

EFFECT OF AGING

Orthostatic hypotension from all causes becomes more prevalent with increasing age.[66] Caird and colleagues studied a large group of ambulatory men and women aged 65 and older.[67] Decreases in systolic blood pressure to 20+ mm Hg below supine resting levels after 1 minute of standing occurred in 24% and decreases of 30+ mm Hg occurred in 9% of the study population. A majority of the subjects had (1) two or more conditions likely to be associated either with hypovolemia or maldistribution of the blood volume (*e.g.*, anemia, chronic infection, or varicose veins) or with impaired cardiovascular control mechanisms (*e.g.*, attributable to treatment with pharmacologic agents having a known potential to cause orthostatic hypotension, such as levodopa, phenothiazines, tricyclic antidepressants, and vasodilators) or (2) presence evidence of structural neuorologic lesions.

Cardiovascular control mechanisms tend to have reduced efficiency even in generally healthy older persons. Changes in arterial pressure produce a smaller heart rate response than in younger subjects, suggesting a blunting of the arterial baroreflex.[68,69] Aging also attenuates responses mediated by β_1-adrenoceptors. There is no conclusive information on the effect of age on α-receptor characteristics and responses to exogenous α-adrenergic stimulation or on humoral mechanisms modulating effector responses (*i.e.*, locally released or circulating prostaglandin, kinins, angiotensin, etc.).[70]

EFFECT OF PHYSICAL FITNESS AND EXERCISE

A possible inverse relationship between physical fitness and orthostatic tolerance has been identified by Klein and co-workers[71] and Stegemann and associates[72] and has been studied extensively. One important reason for this interest is simply that physical fitness is usually perceived as a state with increased ability to withstand

TABLE 2. Postexercise Hemodynamic Data in Six Normal Subjects

Variable	Preexercise Control Value	Postexercise Measurements 5 Minutes	25 Minutes	50 Minutes	110 Minutes
Heart rate (beats per minute)	60	105*	89*	79*	74*
Mean arterial pressure (mm Hg)	94	90*	88*	87*	93
Central venous pressure (mm Hg)	6	4*	3*	4*	4*
Bicarbonate (mmol/liter)	24	15*	20*	23	24
Plasma volume (%)	100	84*	89*	98	100

*$p < 0.05$, compared with control values. All measurements were taken with the subject in the supine position. (Data from Bjurstedt H, Rosenhamer G, Balldin U, et al: Orthostatic reactions during recovery from exhaustive exercise of short duration. Acta Physiol Scand 119:25–31, 1983)

stress, particularly stress in the form of environmental extremes.[71] Decreased orthostatic tolerance is then paradoxic, particularly in a condition associated with expanded blood volume, large heart size, and large functional reserves that could be used to compensate for decreased filling by increased heart rate and peripheral resistance. The paradox has been heightened by the fact that physical deconditioning by bed rest inevitably produces orthostatic intolerance.

Most, but not all,[73] investigators have found fitness-related differences in orthostatic tolerance, but the mechanisms are poorly understood. Early data indicated increased degree of peripheral venous pooling in fit subjects,[74] but later work has provided only limited support for increased venous compliance.[75] Several cross-sectional and longitudinal studies have examined various aspects of baroceptor function. Fit persons have been shown to have attenuated heart rate[71,74,76–78] and vasoconstrictor responses to orthostatic stress.[77–79] Corresponding findings have been made in experimental animals.[80]

Significant group differences in orthostatic tolerance also have been reported in the absence of any major difference in baroreflex function.[81] It is possible that the decreased orthostatic tolerance to a significant extent is a consequence of cardiac mechanics rather than neurohumoral regulatory adaptations. Physical training alters the effective ventricular pressure-volume relationships. Fit subjects are able to respond to increased ventricular filling during exercise with a larger increase in stroke volume than sedentary persons.[35] This implies that the ventricle operates on the steep portion of its pressure–volume curve (see Fig. 5) and that the functionally favorable effect of increased filling is balanced by a correspondingly large decrease in end-diastolic volume and stroke volume when filling pressure decreases in the upright position. A major role of mechanical diastolic mechanisms also may help explain why the very fit and the unfit tend to have orthostatic intolerance whereas there is little or no relationship between tolerance and fitness in the mid range.

The relationship between fitness and orthostatic tolerance has important practical implications in aerospace medicine. Modern high-performance military aircraft are able to withstand considerably higher G-force levels (upward of 9G) than their pilots. A rapid increase in +Gz forces (head-to-foot acceleration) can produce a sudden decrease in cerebral perfusion and sudden loss of consciousness with incapacitation. Full recovery may take as long as 30 seconds with catastrophic consequences.[82,83] Straining maneuvers and isometric muscle activity during acceleration stress can substantially improve G tolerance and require a high level of general fitness, but extreme aerobic fitness may be counterproductive. Optimal exercise training regimens are yet to be defined, although a balanced approach seems preferable. The principal beneficial effect of aerobic exercise, defined as prolonged efforts involving large muscle groups in primarily dynamic exercise, is probably an increase in blood volume. This may be counterbalanced by increased peripheral venous pooling and training effects on diastolic myocardial mechanics. An activity program that promotes both aerobic fitness and the development of skeletal muscle mass and strength has a greater potential to be effective. Convertino and associates[84] have reported favorable effects of a brief bicycle-based training program that produced a modest increase in maximal oxygen uptake, whereas Pawelczyk and co-workers[75] found decreased tolerance after a running program.

Heavy exercise also has acute effects on orthostatic tolerance by producing a combination of transiently increased body temperature, metabolic acidosis, and hypovolemia with reduced central venous pressure and mean arterial pressure (Table 2).[85] This phase is followed by increased orthostatic tolerance, probably due to an expansion of the plasma volume).[86]

HYPERREACTIVE HYPOVOLEMIC ORTHOSTATIC HYPOTENSION

ORTHOSTATIC INTOLERANCE CAUSED BY PROLONGED BED REST AND RELATED CONDITIONS

Prolonged bed rest is a common cause of orthostatic intolerance and decreased exercise performance.[10,87–89] The hemodynamic syndrome is of the hypovolemic hyperreactive variety. There is generally only a modest loss of blood volume (300 to 500 ml), and the degree of hemodynamic abnormality is greater than predicted

from the magnitude of the hypovolemia. The development of cardiovascular dysfunction during bed rest has generally been attributed to the prolonged physical inactivity, but there is now strong support for the concept that a rapid response to the redistribution of body fluids is the primary mechanism.[90-92] Head-down tilt at moderate degrees was first introduced in the Soviet Union as a means of simulating the redistribution of fluids that occurs at zero gravity.[93] A 20- to 24-hour period of tilt at −4° to −6° produces a marked central shift of intravascular and interstitial fluid. Central venous pressure, left ventricular end-diastolic volume, and stroke volume all increase transiently, but the increased central volume promptly activates various compensatory mechanisms. There is also a significant humoral response with inhibition of vasopressin, renin, and aldosterone.[90]

A negative fluid balance is established within hours during head-down tilt. Filling pressures, stroke volume, and cardiac dimensions decrease to a level below the supine baseline within 24 hours.[90-92] In fact, at that time the hemodynamic state in the supine position is similar to that normally prevailing in the upright position. When the system is challenged with an intravenous volume load, the disposition of the infused volume is similar before and after head-down tilt with an equally rapid return to preinfusion intravascular volume in both states despite the significant tilt-induced hypovolemia.[94] This implies that adaptation produces a new operating point for the mechanisms controlling intravascular and interstitial volume. These observations are consistent with Gauer's view (see Blomqvist and Stone[10]) that the upright position defines the normal operating point for the human cardiovascular system. Once adaptation has occurred and supine hemodynamics approach the normal upright pattern, the subject will have lost the capacity to deal with the fluid shift that occurs during the transition from supine to upright position. Orthostatic intolerance becomes manifest. The degree of cardiovascular dysfunction is similar after a 3-week bed rest period and after 20 hours at head-down tilt.[92] A similar sequence of events is likely to occur during adaptation to the microgravity during space flight. Postflight orthostatic intolerance is to some extent present in virtually all returning astronauts. The degree of orthostatic intolerance and the loss of exercise capacity following space flight is also significantly greater than would be predicted from the total blood volume loss. It has been shown that blood volume loss during bed rest can be prevented by the administration of 9α-fluorohydrocortisone or corrected by intravenous fluid administration. Neither intervention completely restores normal hemodynamics.[10] Exercise in the supine position during bed rest does not prevent the development of orthostatic intolerance, whereas a few hours per day spent in the standing or sitting position is an effective countermeasure.[10] Relative short daily periods of LBNP at moderate levels of negative pressure have been shown to be effective in preventing orthostatic intolerance induced by prolonged (120 days) periods of head-down tilt[95] and have also been used routinely by Soviet cosmonauts during long space flights.[96]

The exact regulatory adaptations that are responsible for the disproportionately large effect of the hypovolemia are still to be defined. On the other hand, there is little doubt that the fluid shift is the primary stimulus to the cardiovascular changes that develop during bed rest. This has clinical relevance and provides a rationale for reemphasis of the arm chair approach to the treatment of acute cardiovascular disorders as described by Levine and Lown.[97]

MITRAL VALVE PROLAPSE AND RELATED CONDITIONS

Much attention has been paid to a fairly large, but poorly defined, group of patients with functionally important circulatory abnormalities in the absence of any structural neurologic or major cardiovascular lesions. Symptoms suggesting orthostatic intolerance are common. Other complaints include atypical chest pain, palpitations, fatigue, and poor exercise tolerance. In the absence of any physical or echocardiographic findings of mitral valve prolapse (MVP), these patients are often given diagnosis of dysautonomia, vasoregulatory asthenia,[98] or hyperkinetic heart syndrome[99] or are considered to have cardiovascular symptoms related to anxiety neurosis. Starr[100] suggested that the primary defect in neurocirculatory asthenia is a "clumsiness of the circulation," analogous to the ordinary clumsiness of muscular movements. Clumsiness in a sense of lack of precise control is a prominent feature of the mitral valve prolapse syndrome (MVPS, the combination of prolapse and symptomatic autonomic dysfunction) and related disorders. Some patients with MVPS have either markedly attenuated or grossly enhanced vagally mediated cardiovascular responses to common stimuli, such as the Valsalva maneuver or the diving reflex.[24,101]

Many aspects of MVPS have been examined in great detail.[102] A series of studies by Gaffney, Schutte, and associates have dealt with the nature of the autonomic dysfunction in MVP, including its links to the degree of valulvar abnormality and its relation to similar functional abnormalities in patients without valvular defects.[24,103-106] The combined experience of these investigators has been reviewed.[107]

There is a tenuous relationship between the degree of anatomical abnormality and the severity of any symptoms. The characteristic click–murmur complex is only a marker that reflects an abnormal relationship between valvular and ventricular anatomy. Prolapse can be the consequence of a redundant valve or of reduced left ventricular size. At one extreme is a group of patients with a large valve and associated skeletal defects, including pectus excavatum and scoliosis. Schutte and co-workers described a distinctive habitus in women with MVP.[104] A discriminant function that used only height, arm span, and anteroposterior chest diameter produced correct classification of 75% to 85% of patients with MVP and controls. The combination

of prolapse and these anthropomorphic features is inherited as a dominant trait. On the opposite side of the spectrum are patients who may be symptomatic with chest pain, palpitations, fatigue, exercise intolerance, and marked orthostatic hypotension and who have prolapse with normal valvular anatomy, but a small left ventricle. Furthermore, MVP can be produced in perfectly normal asymptomatic persons by interventions that decrease the size of the left ventricle. Beattie and co-workers performed two-dimensional echocardiograms in 20 normal subjects during LBNP that induced a progressive reduction in left ventricular volume.[108] Almost one third of the subjects developed posterior bowing of the mitral leaflets and fulfilled classic echocardiographic criteria for MVP.

It has been suggested that many patients with prolapse have a primary hyperadrenergic state,[102,109,110] expressed primarily as increased β-adrenergic activity that produces a hyperkinetic circulatory state. However, most of our patients with MVP have had normal levels of plasma catecholamines and normal hemodynamic state during supine rest. The heart rate response to exogenous β-adrenergic stimulation by infusion of isoproterenol is also within normal limits. Some patients show large postural increases in plasma norepinephrine levels, but these persons tend to have large postural decreases in ventricular end-diastolic volume and stroke volume. Massive sympathetic activation with tachycardia and vasoconstriction is necessary to maintain normal blood pressure and cerebral perfusion in the upright position. However, some patients have an exaggerated vasoconstriction and produce blood pressures above control values even in the presence of an abnormally low cardiac output, suggesting true α-adrenergic hyperreactivity. Maintaining a normal activity pattern and spending the day in the upright position, sitting, standing, and walking then produces a chronic hyperadrenergic state.

Hypovolemia is a common feature of the prolapse syndrome. The combination of increased α-adrenergic activity and hypovolemia in MVPS is reminiscent of the findings in patients with pheochromocytoma, in whom excessive cathecholamines cause a volume-contracted state. Other studies in normotensive and hypertensive subjects have also documented a strong, general, inverse relationship between blood volume and the levels of sympathetic stimulation. Increased vascular tone in both arterial and venous systems reliably produces a rapid and marked decrease in total blood volume. The hypovolemia will become chronic if the increase in sympathetic drive persists. Mechanisms by which chronic vasoconstriction, hypovolemia, and MVP and MVPS might interact are presented in Figure 10.

The hypovolemia and MVP combine to magnify the reduction in forward stroke volume that normally occurs during orthostatic stress. A vicious cycle is established when marked vasoconstriction is required to maintain arterial blood pressure and cerebral perfusion in the upright position. Substantial mitral regurgitation is not a prerequisite for an exaggerated postural stroke

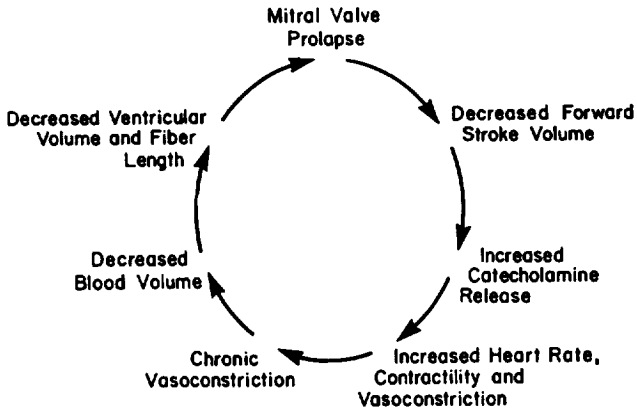

Fig. 10. A proposed set of pathophysiologic mechanisms linking mitral valve prolapse and autonomic nervous system dysfunction in a vicious cycle. A hemodynamically significant prolapse is not a requirement. (Gaffney FA, Blomqvist CG: Mitral valve prolapse and autonomic nervous system dysfunction: A pathophysiological link. In Boudoulas H, Wooley CF (eds): Mitral Valve Prolapse and the Mitral Valve Prolapse Syndrome, pp 427–443. Mount Kisco, NY, Futura Publishing Co, 1988)

volume reduction. The increasing volume contained by the ballooning mitral leaflets with decreasing ventricular size may produce, for any given reduction in left ventricular filling pressure, an exaggerated decrease in diastolic sarcomere length, fiber shortening, and forward stroke volume. These effects are likely to be further amplified by effects of hypovolemia on effective ventricular pressure–volume relationships (see Fig. 5). Measurements based on radionuclide ventriculography have shown marked reduction in left ventricular end-diastolic volume in patients with MVP during upright rest and exercise. This supports the concept that decreased ventricular filling and forward stroke volume in the upright position are critical features in the pathophysiology of this syndrome.[24,107]

This relationship between MVP, reduced blood volume, and chronic vasoconstriction may well provide an explanation for the complex overlap of features in MVP and in a variety of functional and psychiatric syndromes.[108] Excessive vasoconstriction caused by chronic anxiety with elevated catecholamines, high resting heart rates, and diminished plasma and ventricular volumes may produce functional MVP defined as abnormal motion of a structurally normal mitral valve. Similarly, autonomic dysfunction with orthostatic intolerance in patients with myxomatous MVP could be expected to increase the frequency of symptoms, such as palpitations, easy fatigability, near-syncope, and resting tachycardia that often are interpreted as signs of psychoneurosis. Although studies specifically linking anxiety, vasoconstriction, and diminished blood volume are not available, a number of psychophysiologic studies document a strong relationship between acute and chronic stress, anxiety, and vasoconstriction. This relationship forms the rationale for the use of skin temperature as an indicator of the levels of stress and anxiety when training subjects in relaxation

TABLE 3. General Classification of Autonomic Failure

I. Primary
  A. Pure autonomic failure (Bradbury-Eggleston syndrome, formerly idiopathic orthostatic hypotension)
  B. Autonomic failure with multiple system atrophy (Shy-Drager syndrome)
  C. Autonomic failure with Parkinson's disease
II. Secondary
  A. General medical disorders (diabetes, amyloid, carcinoma, alcoholism)
  B. Autoimmune diseases (acute and subacute dysautonomia, Guillain-Barré syndrome, connective tissue diseases)
  C. Metabolic diseases (porphyria, vitamin B_{12} deficiency, Tangier disease, Fabry's disease)
  D. Hereditary disorders (dominant or recessive sensory neuropathies, familial dysautonomia, familial hyperbradykinism)
  E. Central nervous system infections (syphilis, Chagas' disease, herpes zoster, human immunodeficiency virus)
  F. Central nervous system lesions (vascular lesions or tumors involving hypothalamus or midbrain, multiple sclerosis, Wernicke's encephalopathy, Adie's syndrome)
  G. Neurotransmitter defects (Dopamine β-hydroxylase deficiency)
  H. Aging
III. Drugs
  A. Tranquilizers (phenothiazines, barbiturates)
  B. Antidepressants (tricyclics, monoamine oxidase inhibitors)
  C. Vasodilators (nitrates, hydralazine, calcium antagonists)
  D. Adrenergic blocking agents (central or peripheral action)
  E. Angiotensin-converting enzyme inhibitors

(Modified from Bannister R, Mathias C: Management of postural hypotension. In Bannister R (ed): Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 2nd ed, pp 569–595. Oxford, Oxford University Press, 1988)

techniques and biofeedback. There is also evidence that hypovolemia can be found in patients with severe, chronic stress and anxiety directly related to serious somatic disease. The "missing blood syndrome"[111] refers to a profound hypovolemia in wounded Vietnam war casualties undergoing long-term reconstructive treatment. This "anemia" is actually a severe hypovolemia, characterized by a near-normal or even slightly elevated hematocrit. It is resistant to transfusion and iron therapy and is associated with significant hypotension during surgery. It eventually disappears spontaneously when the patient's underlying condition has improved to a point when he otherwise is ready for discharge home.

Fouad and associates[112] have described a previously unknown variety of hypovolemia by studying a group of 11 patients with orthostatic intolerance and a marked reduction (average −27%) in blood volume. Extensive diagnostic studies excluded pheochromocytoma and hypoaldosteronism. The hemodynamic pattern at rest supine was characterized by subnormal cardiac output and high peripheral resistance. The blood pressure tended to be labile, but catecholamine responses to head-up tilt and cardiovascular responses to the Valsalva maneuver, to the cold pressor test, and to exogenous β-adrenergic stimulation were all appropriate. The hemodynamic state at rest was temporarily normalized by blood volume expansion by intravenous human albumin. The syndrome was termed *idiopathic hypovolemia* in the absence of any identifiable cause of the abnormal cardiovascular state.

NORMOVOLEMIC HYPOREACTIVE ORTHOSTATIC HYPOTENSION

There is a wide spectrum of neurogenic causes of orthostatic hypotension. Bannister's[113] classification (Table 3) of autonomic failure includes (1) *primary defects,* in which the disease process is well defined and involves only a limited number of structural elements, (2) *secondary defects,* in which the involvement of the autonomic nervous system is part of a more general process, and, (3) *drug-induced autonomic failure.*

Orthostatic hypotension is often the first symptom of autonomic failure. Bannister suggested that the need for precise postural adjustments of the circulation arose during a late evolutionary stage and that the mechanisms preventing orthostatic cerebral ischemia therefore are less robust than other more basic control systems. However, many patients with autonomic failure present with apparent Parkinson's disease or with bladder symptoms and impotence. Most of the different conditions listed in Table 3 are discussed in great detail in a monograph by Schatz[114] and in Bannister's textbook.[113]

Schatz classified the neurogenic causes with respect to the anatomical site of the principal defect.[114] Involvement of afferent pathways is relatively rare, but occurs in diabetes mellitus, alcoholic neuropathy, and the Holmes-Adie syndrome. Central lesions cause the autonomic failure in familial dysautonomia (Riley-Day syndrome). Multiple cerebral infarcts and Wernicke's encephalopathy may induce autonomic dysfunction with orthostatic hypotension. Mild orthostatic hypotension is also often present in idiopathic parkinsonism.

The majority of the causes of neurogenic orthostatic hypotension primarily involve the efferent pathways of the autonomic nervous system. Pure autonomic failure (formerly idiopathic orthostatic hypotension) is characterized by denervation-type hypersensitivity to direct-acting catecholamines, but decreased response to tyramine and by low peripheral catecholamine stores but increased α-adrenergic receptor density, all of which are features consistent with a postsynaptic lesion. Multiple system atrophy (Shy-Drager syndrome) is a more diffuse degenerative process. Abnormalities have been documented in several areas, including the solitary nucleus and preganglionic vagal neurons. Norepinephrine levels at rest are normal, and the peripheral sympathetic system is probably intact. Spinal cord trauma may affect the function of the intermediolateral column and produce orthostatic hypotension.

Autonomic failure is often generalized in diabetes, and orthostatic hypotension may be a relatively late manifestation. Its emergence is usually caused by sympathetic vasoconstrictor nerve damage. Diabetic neuropathy may also involve afferent pathways. Any peripheral neuropathy may damage the adrenergic

vasoconstrictor nerves. Chronic alcoholism may affect both the afferent and efferent limbs of the autonomic nervous system, but orthostatic hypotension usually occurs late.

TREATMENT OF CHRONIC ORTHOSTATIC HYPOTENSION

THERAPY FOR HYPOVOLEMIC HYPERREACTIVE ORTHOSTATIC HYPOTENSION

The following sequence of care is intended primarily for patients with hypovolemic hypereactive orthostatic hypertension, such as occurs in patients with MVPS[107] and related conditions.

1. Information and reassurance. Many patients with orthostatic hypotension are anxious and should be given a liberal amount of attention with detailed explanations and reassurance.
2. Physical training and increased salt intake. A progressive physical fitness program is often helpful. Physical training causes a balanced increase in plasma volume and red blood cell mass. Adrenergic activity at rest and during submaximal exercise is reduced.[35] However, occasionally patients may have markedly impaired cardiac filling also during exercise.[103] They often have very low exercise capacity and derive little benefit from physical training when it is used as the initial intervention. These patients may respond favorably if exercise is reintroduced at a later stage of treatment. Swimming has been recommended as an ideal form of exercise. The external hydrostatic pressure effectively prevents any activity-induced orthostatic symptoms, but upright water immersion must be avoided since it is a powerful diuretic agent and rapidly induces acute hypovolemia.[10] With these precautions, swimming is appropriate as an initial step, but should progress to a balanced exercise program, designed to improve both aerobic fitness and skeletal muscle mass and strength.

   Many persons have been impressed with the potential dangers of excess sodium chloride. Patients with MVPS, who have symptoms of chest pain and palpitations, may be particularly prone to self-imposed salt restriction, which certainly is not needed in the presence of hypovolemia and low blood pressure. On the other hand, increased salt and fluid intake is rarely effective unless combined with other measures.
3. Low-dose clonidine treatment. Clonidine is an α_2-adrenergic agonist. It also has central effects that usually produce adrenergic inhibition. The onset of the action is gentle, and side-effects are mostly limited to sedation and dryness of the mouth. The α-antagonistic effects usually dominate in subjects with a grossly intact autonomic nervous system, and clonidine has the capacity to break the vicious circle of vasconstriction, hypovolemia, and orthostatic intolerance in patients with MVPS or chronic anxiety.

   Clonidine treatment for at least a month resulted in reduced postural catecholamine responses and relative vasodilatation in the upright position, but markedly improved orthostatic tolerance in a series of 8 patients (Fig. 11) studied by Gaffney and associates.[105] The treatment also caused a 12% expan-

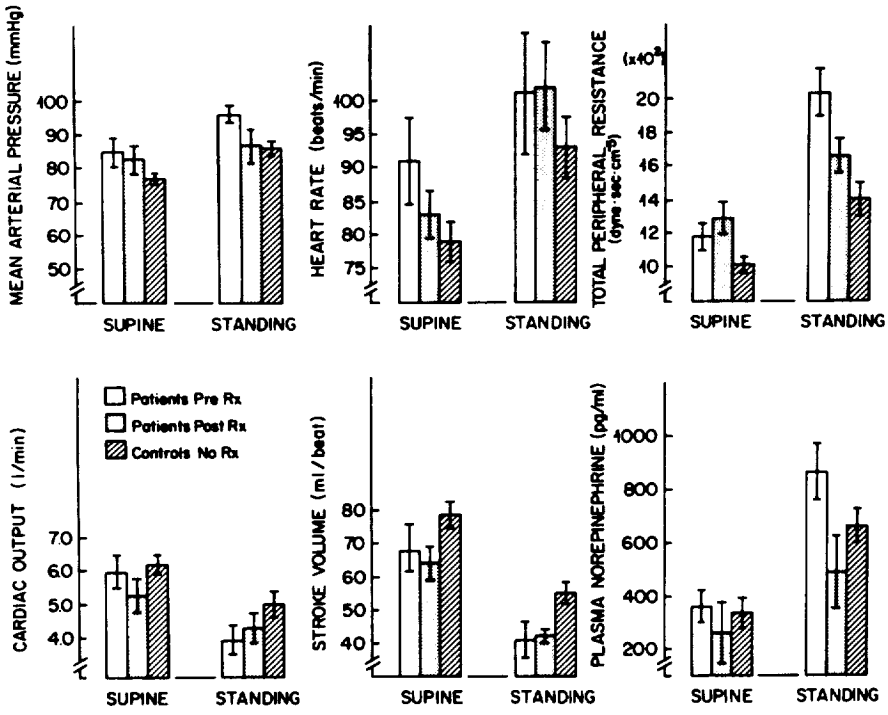

Fig. 11. Hemodynamic and neuroendocrine measurements in controls and in patients before and after long-term oral administration of clonidine (values are means ± SE). (Gaffney FA, Lane LB, Pettinger W et al: Effects of long-term clonidine administration on the hemodynamic and neuroendocrine postural responses of patients with dysautonomia. Chest 83S:436S–438S, 1983)

TABLE 4. Drugs Used in the Treatment of Postural Hypotension

Site of Action	Drugs	Predominant Action
Vessels: vasoconstriction		
Adrenoceptor mediated:		
Resistance vessels	Ephedrine	Indirectly acting sympathomimetic
	Midodrine, phenylephrine, methylphenidate	Directly acting sympathomimetics
	Tyramine	Release of norepinephrine
	Clonidine	Postsynaptic α-adrenoceptor agonist
	Yohimbine	Presynaptic α_2-adrenoceptor antagonist
Capacitance vessels	Dihydroergotamine	Direct action on α-adrenoceptors
Vessels: prevention of vasodilatation	Propranolol	Blockade of β_2-receptors
	Indomethacin	Blockade of prostaglandins
	Metoclopramide	Blockade of dopamine
Vessels: prevention of postprandial hypotension	Caffeine	Blockade of adenosine receptors
	SMS 201-995	Blockade of vasodilator peptides
Heart: stimulation	Pindolol	Intrinsic sympathetic action
	Xamoterol	
Plasma volume expansion	Fludrocortisone	Mineralocorticoid effects
		Increased plasma volume
		Sensitization of α-receptors to norepinephrine
Kidney: reducing diuresis	Desmopressin	Action: V_2-receptors of renal tubules

(Modified from Bannister R, Mathias C: Management of postural hypotension. In Bannister R (ed): Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 2nd ed, pp 569–595. Oxford, Oxford University Press, 1988)

sion of the plasma volume. Significant improvement was evident, measured both by symptoms and by quantitative analysis of the postural hemodynamic responses. Clonidine treatment progressed at 2-day intervals from 0.05 mg orally at bed time to 0.4 mg/day, or to side effects. Coghlan has successfully used a similar regimen at the University of Alabama, Birmingham (personal communication to Dr. Gaffney). The patients with idiopathic hypovolemia studied by Fouad and associates[112] received clonidine in low doses (0.1 to 0.2 mg/day) as an effective adjunct to plasma expansion therapy with hydrofluorocortisone (0.1 mg twice daily) and a diet high in sodium.

Thus, the central adrenergic inhibitory action of clonidine that makes it effective in essential arterial hypertension produces equally beneficial effects in hypovolemic hyperreactive orthostatic hypotension. Clonidine has also proved to be a useful agent in patients with severe idiopathic hypotension and complete loss of peripheral neural sympathetic and parasympathetic control. In these patients, the α_2-agonist properties totally dominate and produce vasoconstriction and venoconstriction with a substantial increase in blood pressure.[115]

4. Progression to the treatment usually reserved for patients with normovolemic hyporeactive orthostatic hypotension is indicated if measures 1 through 3 prove ineffective.

THERAPY FOR NORMOVOLEMIC HYPOREACTIVE ORTHOSTATIC HYPOTENSION

The approach to therapy is generally more complex in the hyporeactive group. It is often very difficult to determine the exact nature, localization, and extent of the underlying disease process. As a consequence, the therapy will often have an empiric component.

Bannister and Mathias[15] have reviewed general principles for management and made several important points. Patients with chronic hyporeactive orthostatic hypotension tend to adjust their autoregulatory range for adequate cerebral blood flow. They are often able to maintain adequate cerebral perfusion at subnormal arterial pressures, such as at systolic levels of about 60 mm Hg compared with 80 mm Hg in most normal subjects. Therapy should therefore be guided by symptoms and signs of cerebral ischemia rather than by the blood pressure. Furthermore, consistently normal pressures in the upright position can often only be maintained at the cost of inducing hypertension in the supine position. Comprehensive approaches to treatment have been formulated by Schatz[114] and by Bannister and Mathias.[15]

GENERAL CONSIDERATIONS AND RECOMMENDATIONS

Trivial stresses can produce symptomatic hypotension in patients lacking essential elements of the blood pressure control system and include straining during micturition or defecation, exposure to a warm environment, and having an ordinary meal. Carbohydrates are more likely to induce hypotension than fats or proteins, perhaps via release of insulin and gastrointestinal hormones with vasodilator properties. Alcohol is prone to cause further vasodilatation. On the other hand, caffeine has been found to minimize postprandial hypotension in a placebo-controlled study.[116] Vasoactive drugs should be avoided. The response to vasodilators is amplified for lack of defense mechanisms and the effects of vasoconstrictors and venoconstric-

tors may be greatly magnified by denervation hypersensitivity.

Most patients with chronic orthostatic hypotension have a definite circadian rhythm with minimal pressures during the morning hours. Head-up tilt during sleep, first proposed by Maclean and Allen,[117] minimizes the redistribution of body fluids that otherwise occurs at night. Normally, the central fluid shift during supine bed rest increases cardiac filling and causes a diuresis with a loss of intravascular and interstitial fluid. These losses, which tend to be abnormally large in patients with autonomic failure, are contained by the use of the head-up tilt. There is often a significant improvement of the blood pressure levels during the day and nocturnal hypertension is avoided. External support, in the form of a custom-fitted counterpressure garment, is quite effective in many patients. The garment is constructed of an elastic mesh of graded firmness to match the postural hydrostatic gradients. The disadvantages of the approach become obvious in a hot climate.

PHARMACOLOGIC APPROACHES

A summary of current pharmacologic approaches is given in Table 4.[15] By the nature of these diseases, most agents have been used only in very small groups of patients, and it is difficult to provide adequate evaluation of any single specific approach. The use of clonidine has been discussed in an earlier section. Dihydroergotamine is a direct-acting α-adrenergic agonist that may preferentially cause venoconstriction. The principal disadvantage is its poor bioavailability. Indomethacin has been used to negate the vasodilator effects of prostaglandin, but may be effective primarily by increasing smooth muscle sensitivity to norepinephrine. Fluorohydrocortisone (fludrocortisone) is the most widely used of all pharmacologic agents for the treatment of orthostatic hypotension. Its multiple actions include plasma volume expansion and sensitization of vascular receptors to pressor amines, perhaps by increasing the number of adrenergic receptors. The initial dose in autonomic failure is 0.1 mg daily.

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